

REMARKS**Claim Amendments**

Prior to this Amendment, Claims 1-171 were canceled and Claims 172-209 were pending. New Claims 210-214 have been added. Thus, Claims 172-214 are currently pending.

Support for new Claim 210 can be found throughout the specification, for example, at page 17, line 28 through page 18, line 2, page 19, line 33 through page 20, line 23 and page 22, lines 1-29.

Claims 211 finds support in, e.g., Claim 173, Claim 212 finds support in, e.g., Claim 174 and Claim 213 finds support in, e.g., Claim 177. Claim 214 finds support in, e.g., Claim 172.

No new matter has been added.

Rejection of Claims 172-184, 186 and 188-192 Under 35 U.S.C. 112, First Paragraph (Written Description)

Claims 172-184, 186 and 188-192 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully traverse the rejection. In addition, Applicants believe that new Claims 210-214 are adequately described by the specification.

The Examiner has rejected Claims 172-184, 186 and 188-192 based on alleged lack of enablement and written description; however, the issues generally revolve around the same argument (enablement will be addressed specifically under the next heading). The examiner appears to agree that the present application enables the claims using one of the disclosed techniques, photolithography, but argues that the other ways to make the claimed invention that are described in the specification do not show how to selectively synthesize amino acids on an array. The Examiner generally repeats the maxim that chemistry is unpredictable and that more showing is necessary to enable the claims. However, Applicants respectfully assert that this statement focuses on the wrong issue. The chemistry of reacting one amino acid with another has been well developed since the 1960s with the advent of Merrifield synthesis (see R. B.

Merrifield, J. Am. Chem. Soc. 85, 2149 (1963)). Also, the means to remove protecting groups was also well developed. The present application claims methods that selectively react amino acids to form different polypeptides in spatially discrete locations on a substrate. The examiner has not shown that the knowledge in the art coupled with the present teachings were insufficient to teach one of skill in the art to make and use the claimed subject matter.

MPEP 2163.02 provides the standard for determining if an application complies with the written description requirement:

An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991).

MPEP 2163.04 shows that the burden to make out a prima facie case of lack of written description is on the examiner and shows how a prima facie case is made.

A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. See, e.g., *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). The examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. The examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Wertheim*, 541 F.2d at 263, 191 USPQ at 97.

* * *

In rejecting a claim, the examiner must set forth express findings of fact which support the lack of written description conclusion (see MPEP § 2163 for examination guidelines pertaining to the written description requirement). These findings should:

(A) Identify the claim limitation at issue; and

(B) Establish a *prima facie* case by providing reasons why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed. A general allegation of "unpredictability in the art" is not a sufficient reason to support a rejection for lack of adequate written

description. A simple statement such as "Applicant has not pointed out where the new (or amended) claim is supported, nor does there appear to be a written description of the claim limitation '____' in the application as filed." may be sufficient where the claim is a new or amended claim, the support for the limitation is not apparent, and applicant has not pointed out where the limitation is supported.

Establishing a Prima Facie Case

The Examiner is required to establish a prima facie case under MPEP 2163.03 (I). Simple statements that the art is unpredictable will not suffice. For example, the Examiner relies on the assertion that the preparation of polypeptide arrays was unpredictable as of the effective filing date. Although the preparation of polypeptide arrays according to the present claims was novel and non-obvious as of the effective filing date, the chemistry was not unpredictable in view of the teachings of the specification and the knowledge of the skilled artisan.

First, the Examiner has provided no evidence regarding the alleged unpredictability of the art as of the effective filing date. Second, the Examiner fails to recognize that polypeptide array synthesis on a support represents one type of solid phase synthesis out of the many that were known at the filing date. Solid phase synthesis refers to preparation of a molecule (such as a polypeptide) while one end is attached to a support. Although the presently claimed polypeptide *arrays* had not previously been prepared on a support, the chemistry of solid phase synthesis of biological polymers was well established as of the effective filing date of the instant application. A skilled artisan could readily apply this technology to prepare polypeptide arrays in light of knowledge of the art and the specification.

As evidence, Applicants are enclosing herewith "Exhibit A", which shows that nearly 300 articles on "solid phase synthesis" in the PubMed database were published on or before June 7, 1989. It is pointed out that these articles on solid phase synthesis include methods of preparing polypeptides and oligonucleotides. Thus, one of ordinary skill in the art would have a large body of work to draw on for the chemical aspects of solid phase synthesis of polypeptides as of the effective filing date of the instant application.

Because many solid phase chemical synthesis techniques were well-established as of the effective filing date, it is only necessary that the application describe the characteristics unique to the application of solid phase synthesis techniques to array preparation. The Examiner erroneously states that “the use of photolithographic technique is critical or essential to practice the instant invention” (Office Action mailed June 2, 2004, page 3, 3rd paragraph). As stated many times in the application and during prosecution, photolithography is one preferred technique for array synthesis, but it is neither crucial nor essential to preparation of a recited polypeptide array. There is a considerable body of case law that states that the claims should not be limited to the preferred embodiment, and therefore, this case law applies here.

The Examiner states that selective activation of regions of a substrate involves new chemistry and is unpredictable. However, this reasoning is incorrect because, as stated above, the chemistry of array preparation (including the selective activation steps) is essentially the same as that of solid phase synthesis techniques, with which one of ordinary skill in the art would have been familiar as of the effective filing date of the instant application (see Exhibit A). The difference between array preparation and conventional solid phase synthesis is, at least, that the areas for reaction are controlled in array preparation so that different polypeptides are formed in different areas.

Thus, the issue with respect to written description is whether the teachings of the instant application provide “sufficient description of a representative number of species by actual reduction to practice [], reduction to drawings [], or by disclosure of relevant, identifying characteristics” (MPEP § 2163). As alleged by the Examiner, the specification provides a detailed example in which photolithography is used in preparing an array (see, for example, page 49, line 15 through page 50, line 35 and page 57, line 25 through page 58, line 30). The photolithography example teaches one of ordinary skill in the art how the combination of an energy source (light) and a barrier (a mask) is used to selectively activate regions of a substrate. This photolithography example is representative of other techniques because it demonstrates how the mask permits the light to interact with certain regions of the substrate and prevents the light from reaching other regions of the substrate. Additional energy sources disclosed by the specification include electron beam irradiation, x-ray irradiation, electric current, electric fields, magnetic fields, chemical agents, heat, laser pumping and microelectrodes (see page 19, line 38

through page 20, line 6, page 21, lines 7-28, page 63, line 33 through page 64, line 5 and page 133, lines 26-38). One of ordinary skill in the art would have known suitable protecting groups for use in conjunction with these energy sources (based on a knowledge of solid phase synthesis and more generally organic synthesis), and barriers for the energy sources were generally known (e.g., an insulator for electric fields and currents and a solvent-tight barrier or channel for chemical agents). According to MPEP § 2163, “what is conventional or well known to one of ordinary skill in the art need not be disclosed in detail” (see *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986)). Thus, there is no requirement that the application reiterate the details of methods that were well known as of the effective filing date, and the specification should be held to fulfill the written description requirement.

In conclusion, the specification describes identifying characteristics of a method of selectively activating regions of a substrate in order to prepare a polypeptide array and Applicants have shown that they considered this to be part of their invention at least as far back as 1989. These identifying characteristics adequately describe the generic method of preparing an array, so that Claims 172-184, 186 and 188-192 and new Claims 210-214 fulfill the written description requirement. Moreover, unlike the claims at issue in the case law cited by the Examiner (*University of Rochester v. Searle & Co., Inc.*, 2004 WL 260813 (Fed. Cir. 2004)), the claimed method does not rely on functional language to describe a product. Instead, the claimed invention is distinguished from the prior art by positive method steps where an amino acid is attached only to certain regions of a substrate. The specification identifies the relevant characteristics for attaching a building block, such as an amino acid monomer, to certain regions of a substrate using an energy source and a mask, and specifically demonstrates how the method is performed when the energy source is light. One of ordinary skill in the art would have immediately understood how the essential features in the example apply, for example, to the additional energy sources disclosed in the specification. In view of MPEP § 2163 and the relevant case law, this description fully meets the written description requirement, such that the rejection should be withdrawn. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 172-184, 186 and 188-192 Under 35 U.S.C. 112, First Paragraph
(Enablement)

Claims 172-184, 186 and 188-192 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse the rejection. In addition, Applicants believe that new Claims 210-214 are adequately enabled by the specification.

The Examiner states that while the specification is enabling for photolithographic techniques, it does not reasonably provide enablement for other techniques. However, “[t]he enablement requirement is met if the description enables any mode of making and using the claimed invention.” See, e.g., *Engel Indus., Inc. v. Lockformer Co.*, 946 F.2d 1528, 1533 (Fed. Cir. 1991). In this situation, Applicants respectfully submit that they have clearly demonstrated the preferred photolithography method in multiple variations and have outlined other methods to make the claimed polypeptide arrays. As such, they are entitled to claim the method of preparing a polypeptide array without limitation to a single synthetic technique.

MPEP 2164.01 sets out the test for enablement.

("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."). A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991)

As set out in MPEP 2164.01(a), there are many factors to consider if an enablement rejection is appropriate and if the experimentation is “undue”. The seminal decision is *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), which set out an eight part test for undue experimentation. The eight Wands factors are:

1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

MPEP 2164.04 shows that the burden is on the examiner to show that the experimentation is undue.

In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

As will be shown below, the Examiner has not presented an adequate showing as to why the claims are not enabled. Applicants respectfully assert that the Examiner has not analyzed all of the *Wands* factors properly and has not provided reasons why the enablement is questioned.

To support the rejection, the Examiner cites seven of the eight *Wands* factors on page 5 of the Office Action mailed June 2, 2004 and discusses five of them.

First, the Examiner alleges that the specification fails to give adequate direction and guidance for synthesizing arrays using techniques other than photolithography. However, the Examiner fails to provide sufficient reasoning to support this allegation. Although the Examiner admits that photolithography allows one to direct light to relatively small and precisely known locations on the substrate, the Examiner does not consider that the specification discloses other means of selecting a relatively small and precisely known location on a substrate for contact with a reagent. For example, the physically divided or etched substrates having surface features such as trenches, v-grooves and mesa structures (page 26, lines 18-26) allow one to direct a solvent (*e.g.*, containing an agent to remove protecting groups) to specific locations on a substrate and then selectively protect or deprotect (activate) these specific locations. Additionally, the use of electrodes or electric fields is shown to be another method to selectively activate regions of the substrate. One of ordinary skill in the art would recognize how, for example, these surface features are used to prepare an array, even without an example specifically demonstrating their use. Thus, the direction and guidance provided by the

specification is sufficient. This photolithography example is representative of other techniques because it demonstrates how the mask permits the light to interact with certain regions of the substrate and prevents the light from reaching other regions of the substrate. Additional energy sources disclosed by the specification include electron beam irradiation, x-ray irradiation, electric current, electric fields, magnetic fields, chemical agents, heat, laser pumping and microelectrodes (see page 19, line 38 through page 20, line 6, page 21, lines 7-28, page 63, line 33 through page 64, line 5 and page 133, lines 26-38). One of ordinary skill in the art would have known suitable protecting groups for use in conjunction with these energy sources (based on a knowledge of solid phase synthesis and more generally organic synthesis, which as established above, were well known as of the effective filing date of the instant application), and barriers for the energy sources were generally known (*e.g.*, an insulator for electric fields and currents and a solvent-tight barrier or channel for chemical agents). Therefore, Applicants have provided adequate direction and guidance for synthesizing arrays.

Second, the Examiner states that the working examples are directed to the use of photolithography in making arrays. Even though the examples relate to the preferred embodiment, in addition to some related chemistry, Applicants note that one of ordinary skill in the art would have immediately recognized that other techniques for activating a region of a substrate proceed analogously. The working examples articulate the sequence of events that occur during array synthesis. The additional disclosure of the specification makes it clear that many energy source and barrier combinations can be substituted for light and a mask. The basic sequence of steps to prepare of an array does not change from combination to combination. Therefore, the working examples provide clear and adequate guidance.

Third, the Examiner states that the claims are open-ended with regard to the method of making the arrays. Applicants respectfully disagree. The instant claims recite very specific method steps and are not open-ended. This comment seems to be directed to the breadth of the claims. "Breadth" is certainly a relative term, and one can take various positions that a certain claim is broad or narrow. However, Applicants suggest that a review of the present claims, which contain multiple and specific steps to construct one type of array (*e.g.*, a polypeptide array) is not overly broad because the type of polymer is specifically defined, and the steps are

limited to coupling and activation of protected amino acids with specific groups in different locations on the array.

Fourth, the Examiner characterizes selective protection or deprotection at the time the invention was made as being difficult or unknown. (Applicants believe that this is in relation to the state of the prior art Wands factor.) While Applicants were the first to use selective protection/deprotection to make an array of polymers, the concept of generalized protection/deprotection chemistry involved in these selective reactions is the same as in conventional techniques. For example, Merrifield polypeptide synthesis, which was first published in 1963 and is incorporated by reference in the instant application, is one example of activation and attachment of an amino acid to a growing polypeptide. There are other solid phase synthesis chemistries to select from. In one example, Applicants employed selectivity in placing reagents at particular locations of the array. Applicants note that the resolution of various protection/deprotection techniques is different; some techniques allow a smaller area to be selected. However, the independent claims (Claims 193 and 210) do not recite the number of positionally defined locations per unit area. Thus, the number of different polypeptides formed per unit area is irrelevant in the independent claims. It is improper for the Examiner to read a limitation into these claims. Regardless of the time needed to achieve a high density of “positionally defined locations” using a particular protection/deprotection technique, (e.g., beams of light, volumes of reagent and current from a microelectrode), such techniques were all readily able to be localized to a small area as of the effective filing date, based on the teachings of the specification. The Examiner has provided no reasoning or evidence to demonstrate that any of the protection/deprotection techniques required undue experimentation. Instead, the Examiner tries to shift the focus to “unpredictable chemistry” in an attempt to claim that the current claims are not enabled. Again, various chemical methods were known to one of skill in the art to perform a polypeptide solid phase synthesis method, so that component was not unpredictable.

Fifth and finally, the Examiner states that the art is inherently unpredictable because organic synthesis of peptide arrays on a substrate is not possible without using other methods, such as masking with barriers. Once again, the Examiner provided no support for this assertion. Moreover, the Examiner’s statement is not understood, because Applicants have coupled the use

of known chemistry with ways to selectively activate an area. There are a multitude of ways to do this and Applicants have disclosed many. If the Examiner refers to chemistry as being unpredictable as the basis for this rejection, then Applicants have already shown that the chemistry is not unpredictable. The need for masking does not render the claimed method unpredictable, as appropriate barriers were known for use with various activation methods (and the behavior of a mask is entirely predictable). Also, as established above, the organic chemistry of solid phase synthesis was well understood as of the effective filing date (see Exhibit A). Thus, because masking techniques and solid phase synthesis techniques were well understood as of the effective filing date, solid phase synthesis involving masking was predictable as of the effective filing date.

The other *Wands* factors that the Examiner did not discuss are: the quantity of experimentation that was necessary, the nature of the invention, the state of the prior art, and the skill of those in the art.

The skill of those in the art has generally been asserted as high, for example, someone with a PhD. and several years of experience. Someone with this experience would know or be able to look up a general text to obtain information on polypeptide solid phase synthesis. They would also be able to review the specification and determine what other ways one could create a polypeptide on a solid support in accordance with the current claims. In addition, as shown in Exhibit A, there were over 300 publications on solid phase synthesis as of the effective filing date, such that a large body of knowledge on the subject was available to one of skill in the art. Therefore, this factor would suggest that there is appropriate enablement for one of skill in the art.

Regarding the state of the prior art and the nature of the invention, Applicants have shown that there was a significant body of art that was directed to the chemistry and it has existed since at least the mid 1960s. Thus, the chemistry was not unpredictable.

In summary, the *Wands* factors cited by the Examiner serve as evidence that the claimed methods were fully enabled as of the effective filing date of the instant application. Although photolithography is a particularly efficient way of protecting or deprotecting an area of a substrate, the other methods shown in the specification also can be used without undue

experimentation. The Examiner has provided only vague assertions without supplying reasoning to support the enablement rejection, and this is improper. In contrast, Applicants have provided a detailed analysis of the *Wands* factors and demonstrated that the claims are enabled, and Applicants respectfully request that the rejection should be withdrawn.

In the Response to Arguments section, the Examiner makes a few other statements regarding enablement and Applicants' previous response. To the extent necessary, Applicants wish to correct the record. The Examiner states that:

As in the Applicants response, the 'photolithographic techniques' are analogous to the other lithographic methods; however the mask has to [be] impermeable to the radiation. However, the specification has not taught the types of masks that can be used with different radiations. And further applicant's arguments techniques other than lithography are also enabled by the specification. However, the specification has not disclosed how the techniques other than lithography are used in the selectively activating regions of the solid surface. Applicant's arguments regarding the 'trenches and V' grooves' are not persuasive, because these limitations would only be useful in maintaining the reagents in certain regions, and not related to the instant claimed method selectively activating regions of the solid surface and synthesis of array of polypeptides as claimed.

Applicants would like to address these statements first by saying that the burden is on the Examiner to show why she doubts the objective truth of the enablement. The Examiner has not presented any evidence or reasonable argument for why one of skill in the art would doubt the objective truth of the enablement. Moreover, the Examiner's statements are incorrect. The issue with impermeable masks is erroneous as the typical masks used in semiconductor manufacture are impermeable to the types of radiation disclosed above, such as electron beam irradiation, x-ray irradiation, electric current, and electric fields. Also, one of skill in the art would know or could readily determine (e.g., from references available as of the effective filing date) what would be impermeable to these known types of radiation. Applicants are not claiming to have invented new radiation that was unknown to those in the art, but have simply provided another use of several types of known radiation.

The Examiner has also stated that v grooves and trenches "would only be useful in maintaining the reagents in certain regions, and not related to the instant claimed method selectively activating regions of the solid surface and synthesis of array of polypeptides as

claimed.” However, keeping the reagents in specific locations is one way to selectively activate a region in that particular embodiment.

The Examiner also states:

Appellant’s arguments regarding the ‘magnetic field’ and ‘microelectrodes’ known at the time the invention was filed, is not persuasive. Because even though the ‘magnetic field’ or the microelectrodes’ are known, they are not related to the chemical synthesis or the prior art has not taught or given motivation to use these different energy sources in solid phase chemical synthesis.

However, Applicants show that the above are just two additional methods that may be used to selectively activate regions on an array. For example, microelectrodes would be used in conjunction with electrolytically-removable protecting groups. As demonstrated by references 11 and 12 on page 3 of Exhibit B, such protecting groups have been known since the early 1970s.

Therefore, the Examiner has not provided credible reasons why she doubts the objective truth of the enablement to overcome her burden. Additionally, the reasons that provided are incorrect for the reasons stated above. In contrast, Applicants have provided a detailed analysis of the *Wands* factors, which clearly show that the claimed invention is enabled. Consequently, Applicants believe the instant claims are fully enabled by the specification. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 172-209 Under Obviousness-Type Double Patenting

Claims 172-209 are rejected under obviousness-type double patenting over claims 1-9 of U.S. Patent No. 6,506,558 and claims 1-54 of U.S. Patent No. 6,379,895. Applicants will evaluate the propriety of these rejections and the submission of a Terminal Disclaimer once otherwise allowable subject matter has been identified by the Examiner.

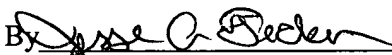
CONCLUSION

Applicants have shown that the Examiner has not met her burden to reject the claims for lack of written description or enablement. Applicants have also shown that they contemplated the presently claimed invention in applications having priority back to June 7, 1989. The Examiner simply repeats the maxim that chemistry is unpredictable and that more showing is necessary to enable the claims. However, Applicants have shown that the chemistry of reacting one amino acid with another has been well developed since the 1960s with the advent of Merrifield synthesis. The present application claims methods that selectively react amino acids to form different polypeptides in positionally defined locations on a substrate. The Examiner has not shown that the knowledge in the art coupled with the present teachings were insufficient to describe the invention or to teach one of skill in the art to produce the claimed subject matter.

If a fee other than the aforementioned fee associated with the Petition for Extension of Time is due with this response, please charge our Deposit Account No. 18-1945, from which the undersigned is authorized to draw, under Order No. AFMX-P03-021.

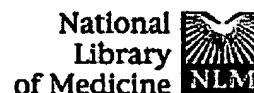
Dated: April 7, 2005

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EXHIBIT A



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Items 1 - 20 of 286

1 of 15 Ne

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☐ 1: [Brunfeldt K, Christensen T, Villemoes P.](#)

[Related Articles, Lin](#)

Automatic monitoring of solid phase synthesis of a decapeptide.
FEBS Lett. 1972 May 1;22(2):238-244. No abstract available.
PMID: 11946606 [PubMed - as supplied by publisher]

☐ 2: [Acevedo OL, Orgel LE.](#)

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Template-directed oligonucleotide ligation on hydroxylapatite.
Nature. 1986 Jun 19;321:790-2.
PMID: 11540863 [PubMed - indexed for MEDLINE]

☐ 3: [Katz BM, Lundquist LJ, Walsh DA, Glass DB.](#)

[Related Articles, Lin](#)

Synthesis, characterization and inhibitory activities of (4-N3[3,5-3H]Phe10) PKI(6-22)amide and its precursors: photoaffinity labeling peptides for the active site of cyclic AMP-dependent protein kinase.
Int J Pept Protein Res. 1989 Jun;33(6):439-45.
PMID: 2550380 [PubMed - indexed for MEDLINE]

☐ 4: [Sakatsume O, Ohitsuki M, Takaku H, Reese CB.](#)

[Related Articles, Lin](#)

Solid phase synthesis of oligoribonucleotides using the 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl (Ctmp) group for the protection of the 2'-hydroxy functions and the H-phosphonate approach.
Nucleic Acids Res. 1989 May 25;17(10):3689-97.
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☐ 5: [Krstensky JL, Payne MH, Owen TJ, Yates MT, Mao SJ.](#)

[Related Articles, Lin](#)

C-terminal peptide alcohol, acid and amide analogs of desulfato hirudin54-6 as antithrombin agents.
Thromb Res. 1989 May 15;54(4):319-25.
PMID: 2763270 [PubMed - indexed for MEDLINE]

☐ 6: [Lehmann C, Xu YZ, Christodoulou C, Tan ZK, Gait MJ.](#)










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Solid-phase synthesis of oligoribonucleotides using 9-fluorenylmethoxycarbonyl (Fmoc) for 5'-hydroxyl protection.
Nucleic Acids Res. 1989 Apr 11;17(7):2379-90.
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☐ 7: [Filippov SA, Esipov DS, Kalinichenko SV, Dobrynin VN.](#)

[Related Articles, Lin](#)

[Synthesis of 5'-phosphorylated oligodeoxyribonucleotides by the H-phosphonate method]
Bioorg Khim. 1989 Apr;15(4):527-9. Russian.
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PMID: 2926144 [PubMed - indexed for MEDLINE]
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PROTECTIVE GROUPS IN ORGANIC SYNTHESIS

THIRD EDITION

Theodora W. Greene

The Rowland Institute for Science

and

Peter G. M. Wuts

Pharmacia and Upjohn Company



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PREFACE

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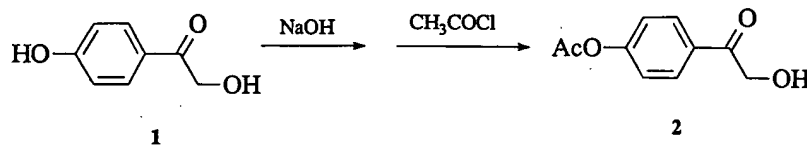
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Organic synthesis has not yet not needed for the synthesis of ment of new methods for fun nues. The new methods added and a manual examination of We have found that electronic new methods that are develop selectivity are often not add attempted to highlight unusual both protection and deprotecti rather redundant, such as the n tection, but we have included t comparison, the first edition of protective groups, the second and 206 new protective groups, 348 new protective groups.

Two new sections on the p included. All other sections of others. The section on the pr reflecting the trend of the nine natural products. An effort was of protection and deprotection. of alcohols as esters and the p attempted to be exhaustive, bu vided that illustrate the true p examine some of the excellent ences. The Reactivity Charts edition. The chart number app when it is first introduced. No a because of the sheer magnitude

HISTORICAL DEVELOPMENT

Since a few protective groups cannot satisfy all these criteria for elaborate substrates, a large number of mutually complementary protective groups are needed and, indeed, are available. In early syntheses, the chemist chose a standard derivative known to be stable to the subsequent reactions. In a synthesis of callistephin chloride, the phenolic—OH group in **1** was selectively protected as an acetate.¹ In the presence of silver ion, the aliphatic hydroxyl group in **2** displaced the bromide ion in a bromoglucoside. In a final step, the acetate group was removed by basic hydrolysis. Other classical methods of cleavage include acidic hydrolysis (eq. 1), reduction (eq. 2) and oxidation (eq. 3):



- (1) $\text{ArO}-\text{R} \rightarrow \text{ArOH}$
- (2) $\text{RO}-\text{CH}_2\text{Ph} \rightarrow \text{ROH}$
- (3) $\text{RNH}-\text{CHO} \rightarrow [\text{RNHCOOH}] \rightarrow \text{RNH}_3^+$

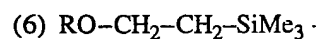
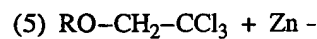
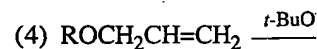
Some of the original work in the carbohydrate area in particular reveals extensive protection of carbonyl and hydroxyl groups. For example, a cyclic diacetone of glucose was selectively cleaved to the monoacetone.² A summary³ describes the selective protection of primary and secondary hydroxyl groups in a synthesis of gentiobiose, carried out in the 1870s, as triphenylmethyl ethers.

DEVELOPMENT OF NEW PROTECTIVE GROUPS

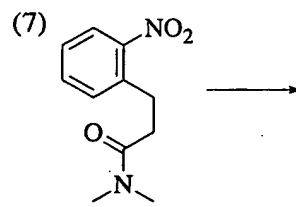
As chemists proceeded to synthesize more complicated structures, they developed more satisfactory protective groups and more effective methods for the formation and cleavage of protected compounds. At first a tetrahydropyranyl acetal was prepared,⁴ by an acid-catalyzed reaction with dihydropyran, to protect a hydroxyl group. The acetal is readily cleaved by mild acid hydrolysis, but formation of this acetal introduces a new stereogenic center. Formation of the 4-methoxytetrahydropyranyl ketal⁵ eliminates this problem.

Catalytic hydrogenolysis of an *O*-benzyl protective group is a mild, selective method introduced by Bergmann and Zervas⁶ to cleave a benzyl carbamate ($>\text{NCO}-\text{OCH}_2\text{C}_6\text{H}_5 \rightarrow >\text{NH}$) prepared to protect an amino group during peptide syntheses. The method has also been used to cleave alkyl benzyl ethers, stable compounds prepared to protect alkyl alcohols; benzyl esters are cleaved by catalytic hydrogenolysis under neutral conditions.

Three selective methods to "assisted," electrolytic, and "assisted removal" of a protective labile vinyl ether group (eq. 6)⁹ derivative is cleaved in phenyl derivative can be readily cleaved by nucleophilic displacement.



R = alkyl, aryl, R'CO—

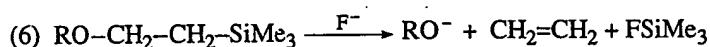
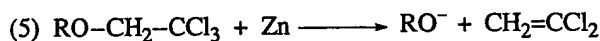


The design of new protective groups is a challenging and rewarding undertaking.

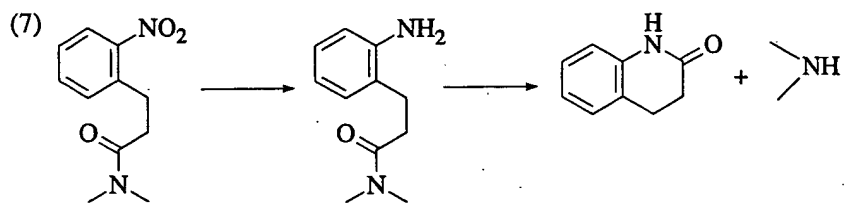
Removal of a protective group in some cases. An advantage of using oxidants or reductants (e.g. Reductive cleavages have been achieved at 1.5–2 V (vs. SCE). Fully labile protective groups with potential differences on been removed by electrolytic cleavage. This book; a chemical removal of protective groups.

Photolytic cleavage reactions (phenylsulfenyl derivatives) to protect a compound for a few hours. A group, used to protect alcohols removed by irradiation. Protective groups are described at the appropriate place. Wish to consult five review articles.

Three selective methods to remove protective groups have received attention: "assisted," electrolytic, and photolytic removal. Four examples illustrate "assisted removal" of a protective group. A stable allyl group can be converted to a labile vinyl ether group (eq. 4)⁷; a β -haloethoxy (eq. 5)⁸ or a β -silylethoxy (eq. 6)⁹ derivative is cleaved by attack at the β -substituent; and a stable *o*-nitrophenyl derivative can be reduced to the *o*-amino compound, which undergoes cleavage by nucleophilic displacement (eq. 7):¹⁰



R = alkyl, aryl, R'CO-, or R'NHCO-



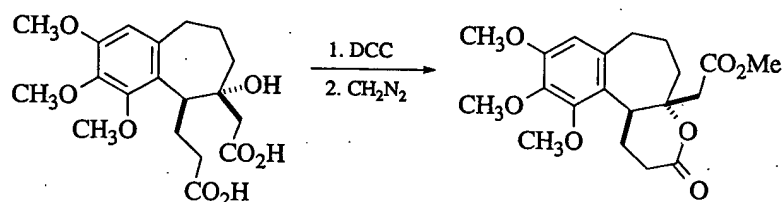
The design of new protective groups that are cleaved by "assisted removal" is a challenging and rewarding undertaking.

Removal of a protective group by electrolytic oxidation or reduction is useful in some cases. An advantage is that the use and subsequent removal of chemical oxidants or reductants (e.g., Cr or Pb salts; Pt- or Pd-C) are eliminated. Reductive cleavages have been carried out in high yield at -1 to -3 V (vs. SCE), depending on the group; oxidative cleavages in good yield have been realized at 1.5-2 V (vs. SCE). For systems possessing two or more electrochemically labile protective groups, selective cleavage is possible when the half-wave potentials, $E_{1/2}$, are sufficiently different; excellent selectivity can be obtained with potential differences on the order of 0.25 V. Protective groups that have been removed by electrolytic oxidation or reduction are described at the appropriate places in this book; a review article by Mairanovsky¹¹ discusses electrochemical removal of protective groups.¹²

Photolytic cleavage reactions (e.g., of *o*-nitrobenzyl, phenacyl, and nitrophenylsulfenyl derivatives) take place in high yield on irradiation of the protected compound for a few hours at 254-350 nm. For example, the *o*-nitrobenzyl group, used to protect alcohols,¹³ amines,¹⁴ and carboxylic acids,¹⁵ has been removed by irradiation. Protective groups that have been removed by photolysis are described at the appropriate places in this book; in addition, the reader may wish to consult five review articles.¹⁶⁻²⁰

One widely used method involving protected compounds is solid-phase synthesis²¹⁻²⁴ (polymer-supported reagents). This method has the advantage of requiring only a simple workup by filtration such as in automated syntheses, especially of polypeptides, oligonucleotides, and oligosaccharides.

Internal protection, used by van Tamelen in a synthesis of colchicine, may be appropriate:²⁵



SELECTION OF A PROTECTIVE GROUP FROM THIS BOOK

To select a specific protective group, the chemist must consider in detail all the reactants, reaction conditions, and functionalities involved in the proposed synthetic scheme. First, he or she must evaluate all functional groups in the reactant to determine those that will be unstable to the desired reaction conditions and that, accordingly, require protection. Then the chemist should examine the reactivities of possible protective groups, listed in the Reactivity Charts, to determine whether the protective group and the reaction conditions are compatible. A guide to these considerations is found in Chapter 10. (The protective groups listed in the Reactivity Charts in that chapter were the most widely used groups at the time the charts were prepared in 1979 in a collaborative effort with other members of Professor Corey's research group.) The chemist should consult the complete list of protective groups in the relevant chapter and consider their properties. It will frequently be advisable to examine the use of one protective group for several functional groups (e.g., a 2,2,2-trichloroethyl group to protect a hydroxyl group as an ether, a carboxylic acid as an ester, and an amino group as a carbamate). When several protective groups are to be removed simultaneously, it may be advantageous to use the same protective group to protect different functional groups (e.g., a benzyl group, removed by hydrogenolysis, to protect an alcohol and a carboxylic acid). When selective removal is required, different classes of protection must be used (e.g., a benzyl ether cleaved by hydrogenolysis, but stable to basic hydrolysis, to protect an alcohol, and an alkyl ester cleaved by basic hydrolysis, but stable to hydrogenolysis, to protect a carboxylic acid). One often overlooked issue in choosing a protective group is that the electronic and steric environments of a given functional group will greatly influence the rates of formation and cleavage. As an obvious example, a tertiary acetate is much more difficult to form or cleave than a primary acetate.

If a satisfactory protective group has not been located, the chemist has a number of alternatives available: rearrange the order of some of the steps in the

synthetic scheme, so that a fit protective group that was reactive in the synthesis, possibly making the group in a precursor form, include the synthesis of a new design new chemistry that avoids

Several books and chapters. Some of these cover the use of protective groups continue three major classes of natural products,²³ and oligonucleotides solid-phase synthesis,²²⁻²⁴ including in the protection and deprotection. Special attention is also called for ethers.³⁰

SYNTHESIS OF COMPLEX EXAMPLES (AS USED IN THE SYNTHESIS OF PALTOTOXIN) OF THE PROTECTION AND REMOVAL OF PROTECTIVE GROUPS

Synthesis of Himastatin

Himastatin, isolated from an *Aspergillus* fungus in Prades State in India and active against a variety of tumor probe system bisindolyl structure in which one half contains a cyclic peptidic structure, L-leucine, D-[(R)-5-hydroxy] and D-valine. The synthesis of himastatin involves the use of protective groups. The synthesis of line moiety A, its conversion to line moiety B, the subsequent cyclization leading to himastatin, and the protective-group aspects of the

Unit A (Scheme 1)

The first objective was the conversion of the carboxyl and hydroxyl groups to pyrrolindolinolines. The carboxyl and hydroxyl groups shown in Scheme 1. A critical trityl group on the NH₂ of the line moiety resulted in stereospecific oxidation and stereochemistry in good yield.

- (2) To cleave the acetonide: 1.18 *N* HClO₄-THF, 25°, 8 days.
- (3) To hydrolyze the acetates and benzoates: 0.08 *N* LiOH/H₂O-MeOH-THF, 25°, 20 h.
- (4) To remove *t*-butyldimethylsilyl (TBS) ethers and the carbamoyl ester (Me₃SiCH₂CH₂OCONHR): Bu₄N⁺F⁻, THF, 22°, 18 h → THF-DMF, 22°, 72 h.
- (5) To hydrolyze the methyl ketal at C.47, no longer stabilized by the C.46 benzoate: HOAc-H₂O, 22°, 36 h.

This order was chosen so that DDQ (dichlorodicyanobenzoquinone) treatment would not oxidize a deprotected allylic alcohol at C.73 and so that the C.47 hemiketal would still be protected (as the ketal) during basic hydrolysis (Step 3).

And so the skillful selection, introduction, and removal of a total of 12 different protective groups has played a major role in the successful total synthesis of palytoxin carboxylic acid (Figure 1, 2).

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